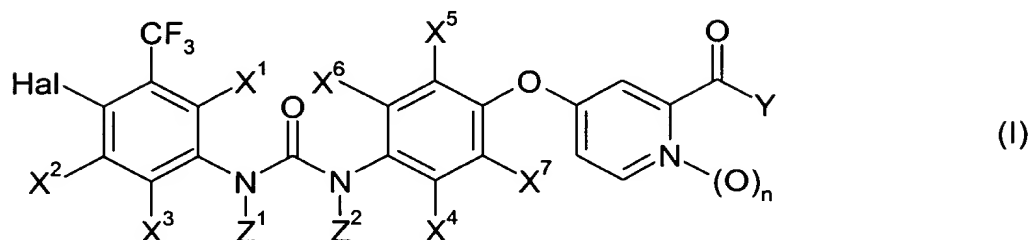


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1. A compound of formula (I),



wherein,

Y is OR^1 or NHR^2 ,

Hal is chlorine or bromine,

R^1 is H or $\text{C}_1\text{-C}_6$ alkyl,

R^2 is H, OH, CH_3 or CH_2OH ,

Z^1 and Z^2 are each H or OH, wherein only one of Z^1 or Z^2 can be OH,

X^1 to X^7 are each, independently, H, OH or $\text{O}(\text{CO})\text{C}_1\text{-C}_4$ alkyl, and

n is 0 or 1,

with the proviso that at least one of conditions a-c is met,

- a) Z^1 or Z^2 is OH,
- b) Y is NHR^2 and R^2 is OH,
- c) n is 1,

or a salt thereof, or an isolated stereoisomer thereof.

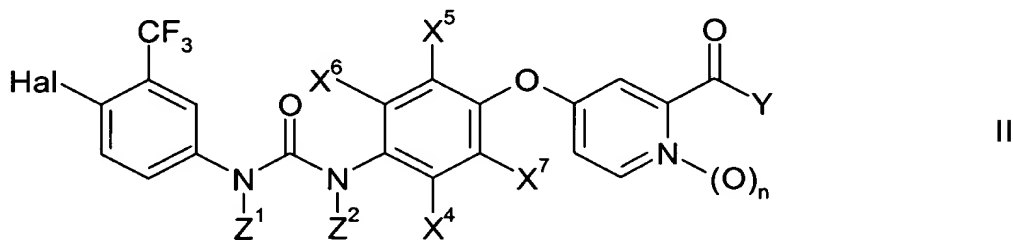
- 2. A compound of claim 1 wherein n of formula I is 1.
- 3. A compound of claim 2 wherein Y is NHR^2 and R^2 is H or CH_3 ,
- 4. A compound of claim 2 wherein
 - a) X^1 to X^7 are each H, or
 - b) Z^1 and Z^2 are each H.
- 5. A compound of claim 2 wherein

- a) X^1 to X^7 are each H, or
 - b) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, or
 - c) X^1 to X^7 and Z^1 are each H and Z^2 is OH or
 - d) X^1 to X^7 and Z^2 are each H and Z^1 is OH.
6. A compound of claim 2, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1$ -
C₄ alkyl.
 7. A compound of claim 2, wherein Y is NHR^2 and R^2 is CH_2OH or OH.
 8. A compound of claim 2 wherein Y is OH.
 9. A compound of claim 1, wherein Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2
is H.
 10. A compound of claim 9, wherein n is 0.
 11. A compound of claim 10, wherein R^2 is H or CH_3 .
 12. A compound of claim 10, wherein X^1 to X^7 are each H.
 13. A compound of claim 10, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1$ -
C₄ alkyl.
 14. A compound of claim 10, wherein R^2 is CH_2OH or OH.
 15. A compound of claim 10, wherein Y is OH.
 16. A compound of claim 1, wherein in formula (I), Y is NHR^2 and R^2 is OH.
 17. A compound of claim 16, wherein n is 0.

18. A compound of claim 17, wherein X^1 to X^7 are each H[.,,].
19. A compound of claim 17, wherein Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H.
20. A compound of claim 17, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1-C_4$ alkyl.
21. A compound of claim 1, wherein in formula (I), Y is OH.
22. A compound of claim 21, wherein n is 0.
23. A compound of claim 22, wherein X^1 to X^7 are each H.
24. A compound of claim 22, wherein Z^2 is H and Z^1 is OH.
25. A compound of claim 22, wherein Z^1 is H and Z^2 is OH.
26. A compound of claim 22, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1-C_4$ alkyl.
27. A compound selected from the group consisting of :
4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide,
4-{4-[(4-bromo-3-(trifluoromethyl)phenyl)amino]carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4-{4-[(4-bromo-3-(trifluoromethyl)phenyl)amino]carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide,
4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide,

4-{4-[[{4-bromo-3-(trifluoromethyl)phenyl}amino}carbonyl]amino]phenoxy}-2-pyridine carboxamide 1-oxide, salts thereof and stereoisomers thereof.

28. A compound of formula (II), or a salt or stereoisomer thereof,



wherein,

Y is OR^1 or NHR^2 ,

Hal is chlorine or bromine,

R^1 is H or $\text{C}_1\text{-C}_6$ alkyl,

R^2 is H, OH, CH_3 or CH_2OH ,

Z^1 and Z^2 are each H or OH, wherein only one of Z^1 or Z^2 is OH,

X^4 to X^7 are each, independently, H, OH or $\text{O}(\text{CO})\text{C}_1\text{-C}_4$ alkyl, and

n is 0 or 1,

with the proviso that at least one of conditions a-c is met,

- a) Z^1 or Z^2 is OH,
- b) Y is NHR^2 and R^2 is OH,
- c) n is 1.

29. A compound of claim 28, wherein in formula (II), n is 1.

30. A compound of claim 29, wherein in formula (II), Z^1 and Z^2 are each H.

31. A compound of claim 30, wherein in formula (II), at least one of X^4 to X^7 is OH.

32. A compound of claim 30, wherein in formula (II), Y is NHR^2 and R^2 is H or CH_3 .

33. A compound of claim 28, wherein in formula (II), n is 0 and Z¹ is H and Z² is OH or Z¹ is OH and Z² is H.

34. A compound of claim 28, wherein in formula (II), n is 0, Z¹ and Z² are each H, and at least one of X⁴ to X⁷ is OH.

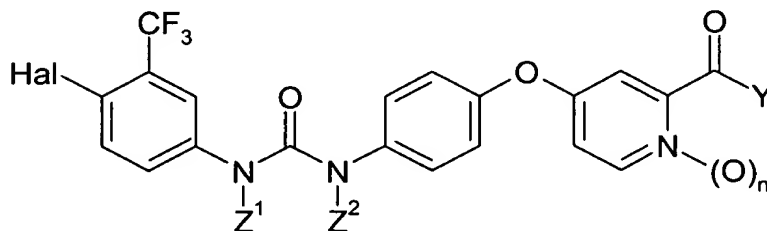
35. A compound of claim 33, wherein in formula (II), at least one of X⁴ to X⁷ is OH.

36. A compound of claim 33, wherein in formula (II), Y is NHR² and R² is H or CH₃.

37. A compound of claim 33, wherein in formula (II) Y is NHR² and R² is OH.

38. A compound of claim 37, wherein in formula (II), at least one of X⁴ to X⁷ is OH.

39. A compound of formula (III), or a salt or isolated stereoisomer thereof,



III

wherein,

Y is OR¹ or NHR²,

Hal is chlorine or bromine,

R¹ is H or C₁-C₆ alkyl,

R² is H, OH, CH₃ or CH₂OH,

Z¹ and Z² are each H or OH, wherein only one of Z¹ or Z² can be OH, and

n is 0 or 1,

with the proviso that at least one of conditions a-c is met,

a) Z¹ or Z² is OH,

- b) Y is NHR^2 and R^2 is OH,
- c) n is 1.

40. A compound of claim 39, wherein in formula (III), n is 1 and Z^1 and Z^2 are each H.

41. A compound of claim 40, wherein in formula (III), Y is NHR^2 and R^2 is H or CH_3 ,

42. A compound of claim 39, wherein in formula (III), n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H,

43. A compound of claim 42, wherein in formula (III), Y is NHR^2 and R^2 is H or CH_3 .

44. A compound of claim 39, wherein in formula (III), Y is OH.

45. A method of preparing compounds of claim 1 comprising the oxidation of 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide, or

4-{4-[({[4-chloro-3-trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide.

46. A method as in claim 45 wherein oxidation of

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[(4-chloro-3-trifluoromethyl)phenyl]amino}carbonylamino]phenoxy}-2-pyridine carboxamide, or

4-{4-[(4-bromo-3-(trifluoromethyl)phenyl]amino}carbonylamino] phenoxy}-2-pyridine carboxamide:

a) replaces one or more of the phenyl hydrogens at the positions represented by X¹ to X⁷ with a hydroxyl group,

b) hydroxylates the N-methyl amide into a hydroxymethyl amide or hydroxamic acid,

c) demethylates the N-methyl amide into an unsubstituted amide,

d) replaces one or more of the urea nitrogens (=NH) with a hydroxyl group to form an N-hydroxyurea (=NOH),

e) hydrolyzes the N-methyl amide into a carboxylic acid,

f) oxidizes the pyridyl ring nitrogen to form the corresponding pyridine-1-oxide,

or

g) provides a combination of two or more of a) - f);

with the proviso that at least one of b), d) and f) is performed.

47. A method as in claim 46 wherein oxidation of

4-{4-[(4-chloro-3-(trifluoromethyl) phenyl]amino}carbonylamino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[(4-bromo-3-(trifluoromethyl) phenyl]amino}carbonylamino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[(4-chloro-3-trifluoromethyl)phenyl]amino}carbonylamino]phenoxy}-2-pyridine carboxamide, or

4-{4-[(4-bromo-3-(trifluoromethyl)phenyl]amino}carbonylamino] phenoxy}-2-pyridine carboxamide replaces one or more hydrogens at the positions represented by X¹ to X⁷ with a hydroxyl group and at least one of the hydroxyl groups in the X¹ to X⁷ positions is esterified.

48. A method as in claim 46 which prepares

4-{4-[(4-chloro-3-(trifluoromethyl) phenyl]amino}carbonylamino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[(4-bromo-3-(trifluoromethyl)phenyl]amino}carbonylamino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,

4-{4-[(4-chloro-3-(trifluoromethyl)phenyl) amino} carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide,

4-{4-[(4-bromo-3-(trifluoromethyl)phenyl) amino} carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide, or a pharmaceutically acceptable salt of one of these oxides, or an isolated stereoisomer of one of these oxides.

49. A pharmaceutical composition comprising an effective amount of at least one compound of claim 1 and a physiologically acceptable carrier.

50. A pharmaceutical composition comprising an effective amount of 4-{4-[(4-chloro-3-(trifluoromethyl) phenyl)amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[(4-bromo-3-(trifluoromethyl)phenyl)amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[(4-chloro-3-(trifluoromethyl)phenyl) amino} carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide, 4-{4-[(4-bromo-3-(trifluoromethyl)phenyl) amino} carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide or a pharmaceutically acceptable salt of one of these oxides, an isolated stereoisomer of one of these oxides or a mixture thereof and a physiologically acceptable carrier.

51. A method of treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of cancer, in a mammal by administering an effective amount of a compound of claim 1 to said mammal.

52. A method as in claim 51 wherein the compound of claim 1 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

53. A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering an effective amount of a compound of claim 1 to said mammal.

54. A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering an effective amount of a compound of claim 27 to said mammal.

55. A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering to said mammal a) an effective amount of a compound of claim 1 and b) an additional anti-proliferative agent.

56. A method as in claim 55 wherein the compound of claim 1 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

57. A method as in claim 56 wherein the pharmaceutical composition comprises an effective amount of a compound of claim 1, a physiologically acceptable carrier and the additional anti-proliferative agent.

58. A method as in claim 56 wherein the additional anti-proliferative agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

59. A method as in claim 56 wherein the additional anti-proliferative agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine,

aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, oxaliplatin, gemcitabone, gefinitib, taxotere, BCNU, CCNU, DTIC, ara A, ara C, herceptin, actinomycin D, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

60. A method of treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of raf-mediated cancer, in a mammal by administering an effective amount of a compound of claim 27 to said mammal.

61. A method of treating or preventing cancer by administering to a mammal

- a) an effective amount of a compound of claim 1, and
- b) a cytotoxic agent or cytostatic chemotherapeutic agent.

62. A method of claim 61 wherein the compound of claim 1 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

63. A method of claim 62 wherein the pharmaceutical composition comprises an effective amount of a compound of claim 1, a physiologically acceptable carrier and the cytotoxic agent or cytostatic chemotherapeutic agent.

64. A method of claim 62 wherein the cytotoxic agent or cytostatic chemotherapeutic agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

65. A method as in claim 61 wherein the cytotoxic or cytostatic chemotherapeutic agent is selected from the group consisting of DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, microtubule disruptors, hormone and growth factor receptor agonists or antagonists, other kinase inhibitors and anti-metabolites.

66. A kit comprising a separate dose of the cytotoxic or cytostatic agent and, a separate dose of a compound of claim 1.

67. A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering to said mammal a) an effective amount of a compound of claim 27 and b) an additional anti-proliferative agent.

68. A method wherein the compound of claim 27 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 27 and a physiologically acceptable carrier.

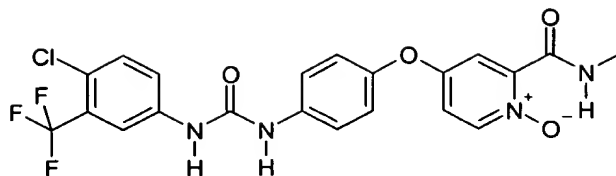
69. A method wherein the pharmaceutical composition comprises an effective amount of a compound of claim 27, a physiologically acceptable carrier and the additional anti-proliferative agent.

70. A method wherein the additional anti-proliferative agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of claim 27 and a physiologically acceptable carrier.

71. A method as in claim 68 wherein the additional anti-proliferative agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycin), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine,

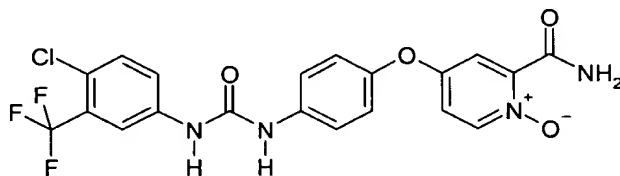
aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, oxaliplatin, gemcitabine, gefinitib, taxotere, BCNU, CCNU, DTIC, ara A, ara C, herceptin, actinomycin D, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

72. A method of preparing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea



comprising chemically oxidizing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} urea in solution.

73. A method of preparing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea



comprising chemically oxidizing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea in solution.